metabolic syndrome [23]: high blood pressure was defined as a systolic blood pressure ≥ 130 mmHg or a diastolic blood pressure ≥ 85 mmHg; dyslipidaemia was defined as serum triglycerides ≥ 1.7 mmol/l or HDL cholesterol < 1.03 mmol/l.

We calculated the incidence rates and hazard ratios (HRs) of diabetes according to the sex-specific quintile of waist circumference and BMI. The Cox proportional hazard model was used to calculate age- and sex-adjusted HRs and multivariate-adjusted HRs. In the multivariate-adjusted model, HRs were adjusted simultaneously for potential confounders including age, sex, family history of diabetes, smoking habits, alcohol use and exercise frequency. In each quintile of waist circumference or BMI, the geometric means of HOMA-IR and HOMA-B were calculated and were compared between those who developed Type 2 diabetes and those who did not using a Student *t*-test. Statistical analysis was conducted with the Statistical Package for the Social Sciences (SPSS version 12.0J; SPSS, Tokyo, Japan).

Results

The baseline characteristics of the study participants are presented in Table 1. At the baseline examinations, the participants had a mean age of 44.4 years for both men and women, a mean BMI of 23.2 kg/m^2 for men and 22.6 kg/m^2 for women and a mean waist circumference of 80.0 cm for men and 72.4 cm for women. During the 8-year follow-up (27 861 person-years), we documented 218 incident cases of diabetes (175 men and 43 women). Among these, 172 were diagnosed with diabetes based on high fasting plasma glucose levels, 40 were diagnosed according to a 75-g OGTT and six had been treated with glucose-lowering medications.

Table 2 shows the baseline characteristics and incidence of diabetes according to the sex-specific quintiles of waist circumference. Participants with higher waist circumference tended to be older and to have higher values of fasting plasma glucose, HbA_{1c}, HOMA-IR and HOMA-B and higher

Table 1 Baseline characteristics of study participants

Characteristic	Total	Men	Women
Participants (*n*)	3992	2533	1459
Age (years)	44.4 ± 5.8	44.4 ± 5.9	44.4 ± 5.7
Waist circumference (cm)	77.2 ± 8.8	80.0 ± 7.6	72.4 ± 8.8
Body mass index (kg/m^2)	23.0 ± 2.9	23.2 ± 2.7	22.6 ± 3.2
Fasting plasma glucose (mmol/l)	5.0 ± 0.49	5.0 ± 0.50	4.9 ± 0.45
Fasting insulin (μU/ml)	5.6 ± 4.3	5.7 ± 4.8	5.4 ± 3.3
HbA_{1c} (%)	5.0 ± 0.4	5.0 ± 0.4	4.9 ± 0.4
HOMA-IR*	1.04 (0.69–1.50)	1.04 (0.67–1.55)	1.03 (0.76–1.43)
HOMA-B*	67.2 (47.0–95.3)	64.5 (43.2–93.3)	72.0 (51.4–98.2)
Systolic blood pressure (mmHg)	119 ± 14	122 ± 14	115 ± 13
Diastolic blood pressure (mmHg)	75 ± 11	77 ± 11	72 ± 10
Total cholesterol (mmol/l)	5.3 ± 0.87	5.3 ± 0.86	5.3 ± 0.89
HDL cholesterol (mmol/l)	1.5 ± 0.40	1.4 ± 0.39	1.7 ± 0.38
Triglycerides (mmol/l)*	1.0 (0.69–1.42)	1.2 (0.80–1.67)	0.8 (0.56–0.99)
Family history of diabetes (%)	11.9	12.8	10.5
Smoking (%)			
Never	53.7	28.7	96.9
Ex-smoker	7.4	11.5	0.5
Current smoker	38.9	59.8	2.6
Alcohol drinking (%)			
Non-drinker	43.8	21.5	82.6
Occasional drinker	2.5	2.2	3.0
Light drinker	41.0	56.9	13.2
Moderate/heavy drinker	12.7	19.3	1.2
Regular exercise (%)			
None	70.9	66.5	78.3
Weak	17.1	19.5	13.2
Moderate	8.8	9.9	6.9
Strong	3.2	4.1	1.6
Prevalence of high blood pressure† (%)	29.5	36.0	18.2
Prevalence of dyslipidaemia† (%)	21.3	29.7	6.8

Values are means ± standard deviation or %.
HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; HOMA-B, homeostasis model assessment of pancreatic B-cell function; HOMA-IR, homeostasis model assessment of insulin resistance.
*Values are geometric means (interquartile range).
†High blood pressure and dyslipidaemia were defined by Japanese criteria of metabolic syndrome.

Table 2 Age- and sex-adjusted and multivariate-adjusted hazard ratios for the incidence of Type 2 diabetes according to sex-specific quintile of waist circumference

	Waist circumference quintile				
Parameter	Q1	Q2	Q3	Q4	Q5
Range of waist circumference, men (cm)	51.0–73.0	73.5–78.0	78.5–82.0	82.5–86.0	86.5–110.0
Range of waist circumference, women (cm)	54.0–65.0	65.5–69.0	69.5–73.5	74.0–80.0	80.5–120.0
Participants (*n*)	852	803	820	765	752
Age (years)	43.7 ± 5.7	44.3 ± 5.7	44.4 ± 5.9	44.7 ± 5.8	45.0 ± 5.9
Fasting plasma glucose (mmol/l)	4.9 ± 0.49	4.9 ± 0.46	5.0 ± 0.46	5.1 ± 0.52	5.1 ± 0.49
HbA_{1c} (%)	5.0 ± 0.4	5.0 ± 0.4	5.0 ± 0.4	5.0 ± 0.4	5.1 ± 0.4
Fasting insulin (μU/ml)	4.1 ± 3.9	4.7 ± 3.4	5.3 ± 3.3	6.3 ± 4.0	7.7 ± 5.7
HOMA-IR*	0.75 (0.54–1.05)	0.88 (0.61–1.24)	1.04 (0.72–1.46)	1.22 (0.86–1.67)	1.48 (1.07–2.06)
HOMA-B*	53.4 (37.9–75.0)	60.2 (41.5–83.5)	66.8 (48.0–90.0)	75.0 (53.3–106.7)	87.9 (63.5–120.0)
Family history of diabetes (%)	10.7	11.7	13.3	10.2	13.8
Prevalence of high blood pressure† (%)	21.5	24.8	28.4	35.6	38.7
Prevalence of dyslipidaemia† (%)	7.9	14.8	21.5	26.0	38.7
Total person-years	6143	5787	5689	5242	5000
Incident cases (*n*)	39	23	34	58	64
Rate per 1000 person-years	6.3	4.0	6.0	11.1	12.8
Adjusted hazard ratio (95% CI) (Model 1)	1.78 (1.06–2.98)	1.00 (reference)	1.59 (0.94–2.71)	3.11 (1.92–5.04)	3.30 (2.05–5.31)
Adjusted hazard ratio (95% CI) (Model 2)	1.81 (1.08–3.04)	1.00 (reference)	1.62 (0.95–2.76)	3.27 (2.01–5.31)	3.37 (2.09–5.43)
Adjusted hazard ratio (95% CI) (Model 3)	1.90 (1.13–3.19)	1.00 (reference)	1.50 (0.88–2.56)	2.82 (1.73–4.61)	2.72 (1.67–4.42)
Adjusted hazard ratio (95% CI) (Model 4)	1.62 (0.96–2.72)	1.00 (reference)	1.18 (0.69–2.01)	2.10 (1.28–3.46)	2.03 (1.24–3.33)

Model 1, adjusted for age and sex; Model 2, adjusted for age, sex, family history of diabetes, smoking, alcohol drinking and habitual exercise; Model 3, adjusted for variables used in Model 2 and presence of hypertension and hyperlipidaemia at baseline; Model 4, adjusted for variables used in Model 3 and fasting plasma glucose level.
CI, confidence interval; HbA_{1c}, glycated haemoglobin; HOMA-B, homeostasis model assessment of pancreatic B-cell function; HOMA-IR, homeostasis model assessment of insulin resistance.
*Values are geometric means (interquartile range).
†High blood pressure and dyslipidaemia were defined by Japanese criteria of metabolic syndrome.

prevalence of high blood pressure and dyslipidaemia (*P* for trend < 0.001 for all). There was no significant difference in prevalence of family history of diabetes among the quintiles of waist circumference.

The crude incident rates (per 1000 person-years) across the sex-specific quintiles of waist circumference at baseline were 6.3, 4.0, 6.0, 11.1 and 12.8, respectively [Table 2]. The association between waist circumference and the incidence of diabetes was J-shaped. The age- and sex-adjusted HRs (Model 1) across the quintiles of waist circumference were 1.78, 1.00 (reference), 1.59, 3.11 and 3.30, respectively, and the HRs of the lowest, the fourth and the highest quintile of waist circumference were significantly higher than that of the second quintile. Further adjustment for family history of diabetes, alcohol intake, smoking and physical activity (Model 2) and the presence of high blood pressure and dyslipidaemia at baseline (Model 3) did not change the HRs. The association became slightly weaker after an additional adjustment for fasting plasma glucose at the baseline examination (Model 4). The results were similar for the association between baseline BMI and the incidence of diabetes [Table 3]. The age- and sex-adjusted HRs across the quintiles of BMI were 1.40, 1.00 (reference), 1.21, 1.97 and 3.06, but the association was somewhat weaker than that for waist circumference. The HR for the lowest quintile was not significantly higher than that for the second quintile. Additional adjustments for potential confounders did not substantially change the HRs (Models 2–4). The results were similar when we excluded the 21 participants who developed diabetes within 1 year of follow-up.

We compared the differences in baseline insulin resistance and pancreatic B-cell function between the participants who developed diabetes and those who did not and examined their association with obesity [Table 4]. Among participants in the lowest and the second waist circumference quintile, HOMA-B was significantly lower in those who developed diabetes than in those who did not; however, there were no differences in HOMA-IR between these two groups. In contrast, among participants in the fourth and the highest quintile of waist circumference, HOMA-IR was significantly higher in those who developed diabetes than in those who did not and no significant difference was observed in HOMA-B between these groups. These relationships were somewhat weaker for BMI.

Discussion

In this prospective cohort study of Japanese men and women, there was a J-shaped association between abdominal obesity and the incidence of Type 2 diabetes. The risk of the lowest quintile

Table 3 Age- and sex-adjusted and multivariate-adjusted hazard ratios for incidence of Type 2 diabetes according to sex-specific quintile of body mass index

Parameter	Body mass index quintile				
	Q1	Q2	Q3	Q4	Q5
Range of body mass index, men (kg/m^2)	15.8–20.9	21.0–22.4	22.5–23.8	23.9–25.4	25.5–33.9
Range of body mass index, women (kg/m^2)	15.2–19.9	20.0–21.4	21.5–22.8	22.9–24.9	25.0–41.3
Participants (*n*)	807	813	790	799	783
Age (years)	43.5 ± 5.6	44.1 ± 5.9	44.7 ± 5.8	44.8 ± 5.8	44.9 ± 5.9
Fasting plasma glucose (mmol/l)	4.9 ± 0.50	4.9 ± 0.47	5.0 ± 0.49	5.0 ± 0.48	5.1 ± 0.49
HbA_{1c} (%)	5.0 ± 0.4	5.0 ± 0.4	5.0 ± 0.4	5.0 ± 0.4	5.1 ± 0.4
Fasting insulin (μU/ml)	4.0 ± 3.0	4.7 ± 3.7	5.5 ± 4.0	6.1 ± 4.9	7.7 ± 4.7
HOMA-IR*	0.75 (0.54–1.06)	0.88 (0.63–1.20)	1.04 (0.74–1.48)	1.16 (0.82–1.61)	1.51 (1.08–2.11)
HOMA-B*	53.1 (37.2–72.0)	59.3 (41.5–83.1)	68.1 (49.1–94.7)	72.2 (51.4–98.5)	89.2 (65.5–120.0)
Family history of diabetes (%)	11.6	12.1	10.6	10.5	14.8
Prevalence of high blood pressure† (%)	22.4	23.5	28.4	32.7	41.0
Prevalence of dyslipidaemia† (%)	9.4	15.1	19.0	26.3	37.4
Total person-years	5781	5836	5492	5518	5234
Incident cases (*n*)	36	27	31	50	74
Rate per 1000 person-years	6.2	4.6	5.6	9.1	14.1
Adjusted hazard ratio (95% CI) (Model 1)	1.40 (0.85–2.30)	1.00 (reference)	1.21 (0.72–2.03)	1.97 (1.23–3.14)	3.06 (1.97–4.75)
Adjusted hazard ratio (95% CI) (Model 2)	1.36 (0.82–2.24)	1.00 (reference)	1.23 (0.74–2.07)	2.02 (1.26–3.23)	3.00 (1.93–4.67)
Adjusted hazard ratio (95% CI) (Model 3)	1.42 (0.86–2.35)	1.00 (reference)	1.18 (0.70–1.98)	1.78 (1.11–2.85)	2.46 (1.57–3.86)
Adjusted hazard ratio (95% CI) (Model 4)	1.27 (0.77–2.10)	1.00 (reference)	1.03 (0.61–1.73)	1.59 (0.99–2.56)	2.06 (1.31–3.24)

Model 1, adjusted for age and sex; Model 2, adjusted for age, sex, family history of diabetes, smoking, alcohol drinking and habitual exercise; Model 3, adjusted for variables used in Model 2 and presence of hypertension and dyslipidaemia at baseline; Model 4, adjusted for variables used in Model 3 and fasting plasma glucose level.
CI, confidence interval; HbA_{1c}, glycated haemoglobin; HOMA-B, homeostasis model assessment of pancreatic B-cell function; HOMA-IR, homeostasis model assessment of insulin resistance.
*Values are geometric means (interquartile range).
†High blood pressure and dyslipidaemia were defined by Japanese criteria of metabolic syndrome.

Table 4 Difference in baseline HOMA-IR and HOMA-B between subjects who developed Type 2 diabetes and those who did not, across the sex-specific quintile of baseline waist circumference or body mass index

	HOMA-IR			HOMA-B		
	No diabetes	Incident diabetes	P*	No diabetes	Incident diabetes	P*
Waist circumference quintile						
Q1 (lowest)	0.75 (0.54–1.05)	0.79 (0.48–1.08)	0.561	54.8 (38.6–75.8)	31.7 (23.2–40.0)	< 0.001
Q2	0.88 (0.62–1.24)	1.03 (0.76–1.35)	0.158	61.1 (42.4–85.0)	36.2 (25.7–51.4)	< 0.001
Q3	1.03 (0.71–1.45)	1.23 (0.82–1.78)	0.041	67.4 (48.2–90.0)	54.0 (34.1–84.0)	0.053
Q4	1.20 (0.86–1.64)	1.59 (1.01–2.28)	0.003	76.4 (55.4–108.0)	60.1 (32.7–99.4)	0.025
Q5 (highest)	1.45 (1.30–2.02)	1.89 (1.34–2.57)	< 0.001	88.9 (65.5–120.0)	78.1 (50.1–106.5)	0.070
Body mass index quintile						
Q1 (lowest)	0.75 (0.54–1.04)	0.83 (0.50–1.15)	0.268	54.3 (37.9–74.6)	33.1 (24.1–45.0)	< 0.001
Q2	0.88 (0.63–1.20)	0.99 (0.71–1.33)	0.226	60.4 (42.4–83.1)	34.8 (23.2–51.4)	< 0.001
Q3	1.04 (0.73–1.48)	1.15 (0.78–1.54)	0.322	68.9 (49.7–94.7)	50.0 (30.0–74.5)	0.001
Q4	1.15 (0.81–1.61)	1.31 (0.85–1.80)	0.111	73.3 (53.3–99.8)	56.9 (35.0–85.5)	0.038
Q5 (highest)	1.46 (1.04–2.04)	2.12 (1.54–2.95)	< 0.001	90.2 (65.7–120.0)	80.0 (53.7–111.7)	0.087

Values are geometric means (interquartile range).
HOMA-B, homeostasis model assessment of pancreatic B-cell function; HOMA-IR, homeostasis model assessment of insulin resistance.
*Student's *t*-test was used to compare geometric means.

of waist circumference was approximately 80% higher than that for the second quintile, indicating that very lean Japanese individuals are also at high risk for developing diabetes. Among the lean participants, HOMA-B was lower in those who developed diabetes than in those who did not, but there was no difference in HOMA-IR between these two groups. These results suggest that lower B-cell function increases the future risk for developing Type 2 diabetes in lean Japanese people with a very low waist circumference, whereas insulin resistance increases the risk in abdominally obese Japanese individuals.

Previous studies have shown that waist circumference is associated with increased risk for diabetes, independently of BMI, and that waist circumference is a better predictor for diabetes than BMI [1,2,6]. Waist circumference is regarded as a more useful marker for insulin resistance and metabolic abnormalities, because it is more closely associated with visceral adiposity, compared with BMI [24]. Our results show that, in obese people, waist circumference was more strongly associated with the future risk for Type 2 diabetes, compared with BMI, and that waist circumference could effectively predict the higher diabetic risk of obese people.

In contrast, previous studies using populations from Western countries have shown that the association between waist circumference and the incidence of Type 2 diabetes was linear, not J-shaped [1–5]. This discrepancy might have resulted from a difference in the degree of obesity between Western and Asian populations. In our study, the upper limit of waist circumference in the lowest quintile was 73 cm for men and 65 cm for women, which was lower than that in previous studies [1–5]. These previous studies might have been unable to detect a higher risk for developing diabetes in people with very low waist circumference.

Racial differences in the association between obesity and the risk for Type 2 diabetes might also have influenced the results. Although the prevalence of obesity is much lower in Asia than in Western countries, the prevalence of Type 2 diabetes is similar between the two regions [8] and Type 2 diabetes occurs in Asians who are less obese [25,26]. In this study, the range of waist circumference in the fourth quintile was 82.5–86.0 cm for men and 74.0–80.0 cm for women; these values were somewhat lower than the cut-off points of waist circumference proposed by the Japan Medical Association (85 cm for men and 90 cm for women) [23] and also by the International Diabetes Federation (90 cm for men and 80 cm for women) [27]. However, multivariate-adjusted hazard ratios for diabetes in the fourth quintile were significantly higher than those in the second quintile. Thus, participants with high–normal waist circumference would also be at high risk for diabetes even although they were not classified as having abdominal obesity. The definition of abdominal obesity in Asians should be carefully considered from the standpoint not only of identifying the people with cardiovascular disease risk factors as proposed by several previous reports [28–32], but also to detect people at higher risk of future diabetes. It has also been reported that the incidence of Type 2 diabetes was significantly higher in Asian women than in non-Hispanic white women after adjustment for BMI [33]. Some factors beyond obesity, including genetics, may also cause the higher risk for Type 2 diabetes seen in Asian populations.

More Asians have prominent abdominal obesity, compared with those in Western countries with a similar BMI [9,10], indicating that Asians may have a higher predisposition to insulin resistance and thus may be at higher risk for developing diabetes at a lower BMI, compared with people of European descent. Furthermore, not only insulin resistance but also impaired pancreatic B-cell function has been reported to play an important role in the development of Type 2 diabetes in Asians [14,34]. We have shown that lower B-cell function may increase the risk for developing diabetes in lean Japanese individuals. Lower B-cell function may cause hyperglycaemia or marked insulin resistance in the absence of abdominal obesity in these very lean participants.

A study conducted in a relatively lean Taiwanese population found that waist circumference for men and BMI for women were strongly associated with the incidence of diabetes [11]; however, the shape of the relationship could not be determined because the data were analysed using linear logistic regression analysis. Recently, a J-curve association between BMI and the incidence of diabetes was reported in Japanese men and women, aged 60–79 years [16]. It was concluded that aging was a high risk factor for developing diabetes, because it is associated with a decline in B-cell function [35,36]; however, our results suggest that younger and leaner individuals with decreased B-cell function may also be at increased risk for developing diabetes mellitus.

The strength of our study lies in its relatively large sample size compared with those of other Asian studies. Many previous cohort studies used information collected from self-administered questionnaires, whereas our conclusions are based on more reliable data obtained from medical examinations and from determinations of fasting blood glucose and insulin levels, HOMA-IR and HOMA-B. However, our study sample included only people who were employed. As poor health may exclude some individuals from working, the prevalence of obesity and the incidence of diabetes may be lower in our sample population than in the general Japanese population. Another limitation of this study was that the classification of diabetes was not precisely determined in all participants with diabetes. Some lean people with diabetes may not have Type 2 diabetes, but Type 1 diabetes or secondary diabetes. However, the participants with incident diabetes in this study were diagnosed in annual medical check-ups with relatively mild hyperglycaemia (mean HbA_{1c} at diagnosis was 5.9% and there was no difference between the quintiles of waist circumference). Furthermore, the results were similar when we determined the risk of diabetes in participants, excluding those who developed diabetes within 1 year of follow-up, who could have other diseases which may influence anthropometric variables and glucose tolerance. Therefore, most of participants who developed diabetes in this study would have Type 2 diabetes.

In conclusion, although the absolute incident risk of diabetes is higher in obese people, leaner Japanese individuals with a smaller waist circumference would also be at high risk for developing Type 2 diabetes. Moreover, lower B-cell function, but not insulin resistance, may increase the future risk of Type 2 diabetes. Greater attention should be given to very lean Asians, in addition to obese Asians, for the primary prevention of Type 2 diabetes.

Competing interests

Nothing to declare.

References

1 Carey VJ, Walters EE, Colditz GA, Solomon CG, Willett WC, Rosner BA *et al.* Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. The Nurses' Health Study. *Am J Epidemiol* 1997; **145**: 614–619.

2 Wei M, Gaskill SP, Haffner SM, Stern MP. Waist circumference as the best predictor of non-insulin-dependent diabetes mellitus (NIDDM) compared to body mass index, waist/hip ratio and other anthropometric measurements in Mexican Americans: a 7-year prospective study. *Obes Res* 1997; **5**: 16–23.

3 Folsom AR, Kushi LH, Anderson KE, Mink PJ, Olson JE, Hong CP *et al.* Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. *Arch Intern Med* 2000; **160**: 2117–2128.

4 Wang Y, Rimm EB, Stampfer MJ, Willett WC, Hu FB. Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. *Am J Clin Nutr* 2005; **81**: 555–563.

5 Meisinger C, Doring A, Thorand B, Heier M, Lowel H. Body fat distribution and risk of type 2 diabetes in the general population: are there differences between men and women? The MONICA/KORA Augsburg cohort study. *Am J Clin Nutr* 2006; **84**: 483–489.

6 The Diabetes Prevention Program Research Group. Relationship of body size and shape to the development of diabetes in the diabetes prevention program. *Obesity* 2006; **14**: 2107–2117.

7 Colditz GA, Willett WC, Stampfer MJ, Manson JE, Hennekens CH, Arky RA *et al.* Weight as a risk factor for clinical diabetes in women. *Am J Epidemiol* 1990; **132**: 501–513.

8 Yoon KH, Lee JH, Kim JW, Cho JH, Choi YH, Ko SH *et al.* Epidemic obesity and type 2 diabetes in Asia. *Lancet* 2006; **368**: 1681–1688.

9 Park YW, Allison DB, Heymsfield SB, Gallagher D. Larger amounts of visceral adipose tissue in Asian Americans. *Obes Res* 2001; **9**: 381–387.

10 He Q, Horlick M, Thornton J, Wang J, Pierson RN Jr, Heshka S *et al.* Sex and race differences in fat distribution among Asian, African-American and Caucasian prepubertal children. *J Clin Endocrinol Metab* 2002; **87**: 2164–2170.

11 Wang SL, Pan WH, Hwu CM, Ho LT, Lo CH, Lin SL *et al.* Incidence of NIDDM and the effects of gender, obesity and hyperinsulinaemia in Taiwan. *Diabetologia* 1997; **40**: 1431–1438.

12 Chen KW, Boyko EJ, Bergstrom RW, Leonetti DL, Newell-Morris L, Wahl PW *et al.* Earlier appearance of impaired insulin secretion than of visceral adiposity in the pathogenesis of NIDDM. Five-year follow-up of initially non-diabetic Japanese-American men. *Diabetes Care* 1995; **18**: 747–753.

13 Matsumoto K, Miyake S, Yano M, Ueki Y, Yamaguchi Y, Akazawa S *et al.* Glucose tolerance, insulin secretion, and insulin sensitivity in non-obese and obese Japanese subjects. *Diabetes Care* 1997; **20**: 1562–1568.

14 Yoshinaga H, Kosaka K. Heterogeneous relationship of early insulin response and fasting insulin level with development of non-insulin-dependent diabetes mellitus in non-diabetic Japanese subjects with or without obesity. *Diabetes Res Clin Pract* 1999; **44**: 129–136.

15 Fukushima M, Suzuki H, Seino Y. Insulin secretion capacity in the development from normal glucose tolerance to type 2 diabetes. *Diabetes Res Clin Pract* 2004; **66**: S37–S43.

16 Sairenchi T, Iso H, Irie F, Fukasawa N, Ota H, Muto T. Underweight as a predictor of diabetes mellitus in older adults: A large cohort study. *Diabetes Care* 2008; **31**: 583–584.

17 Morikawa Y, Nakagawa H, Ishizaki M, Tabata M, Nishijo M, Miura K *et al.* Ten-year follow-up study on the relation between the development of non-insulin-dependent diabetes mellitus and occupation. *Am J Ind Med* 1997; **31**: 80–84.

18 Ishizaki M, Yamada Y, Morikawa Y, Noborisaka Y, Ishida M, Miura K *et al.* The relationship between waist-to-hip ratio and occupational status and lifestyle factors among middle-aged male and female Japanese workers. *Occup Med (Lond)* 1999; **49**: 177–182.

19 Sakurai M, Miura K, Takamura T, Ota T, Ishizaki M, Morikawa Y *et al.* Gender differences in the association between anthropometric indices of obesity and blood pressure in Japanese. *Hypertens Res* 2006; **29**: 75–80.

20 Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**: 412–419.

21 American Diabetes Association. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997; **20**: 1183–1197.

22 Kuzuya T, Nakagawa S, Satoh J, Kanazawa Y, Iwamoto Y, Kobayashi M *et al.* Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. *Diabetes Res Clin Pract* 2002; **55**: 65–85.

23 Japan Medical Association Examination Committee of Criteria for Metabolic Syndrome. Definition and criteria of metabolic syndrome. *J Jpn Soc Int Med* 2005; **94**: 794–809.

24 Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J *et al.* Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol* 2004; **97**: 2333–2338.

25 Ko GT, Chan JC, Cockram CS, Woo J. Prediction of hypertension, diabetes, dyslipidaemia or albuminuria using simple anthropometric indexes in Hong Kong Chinese. *Int J Obes Relat Metab Disord* 1999; **23**: 1136–1142.

26 Sone H, Ito H, Ohashi Y, Akanuma Y, Yamada N. Obesity and type 2 diabetes in Japanese patients. *Lancet* 2003; **361**: 85.

27 Alberti KG, Zimmet P, Shaw J for the IDF Epidemiology Task Force Consensus Group. The metabolic syndrome—a new worldwide definition. *Lancet* 2005; **366**: 1059–1062.

28 Hara K, Matsushita Y, Horikoshi M, Yoshiike N, Yokoyama T, Tanaka H *et al.* A proposal for the cut-off point of waist circumference for the diagnosis of metabolic syndrome in the Japanese population. *Diabetes Care* 2006; **29**: 1123–1124.

29 Ohkubo T, Kikuya M, Asayama K. A proposal for the cut-off point of waist circumference for the diagnosis of metabolic syndrome in the Japanese population. *Diabetes Care* 2006; **29**: 1986–1987.

30 Matoba Y, Inoguchi T, Nasu S, Suzuki S, Yanase T, Nawata H *et al.* Optimal cut points of waist circumference for the clinical diagnosis of metabolic syndrome in the Japanese population. *Diabetes Care* 2008; **31**: 590–592.

31 Oka R, Kobayashi J, Yagi K, Tanii H, Miyamoto S, Asano A *et al.* Reassessment of the cutoff values of waist circumference and visceral fat area for identifying Japanese subjects at risk for the metabolic syndrome. *Diabetes Res Clin Pract* 2008; **79**: 474–481.

32 Narisawa S, Nakamura K, Kato K, Yamada K, Sasaki J, Yamamoto M. Appropriate waist circumference cutoff values for persons with multiple cardiovascular risk factors in Japan: a large cross-sectional study. *J Epidemiol* 2008; **18**: 37–42.

33 Shai I, Jiang R, Manson JE, Stampfer MJ, Willett WC, Colditz GA *et al.* Ethnicity, obesity, and risk of type 2 diabetes in women: a 20-year follow-up study. *Diabetes Care* 2006; **29**: 1585–1590.

34 Kadowaki T, Yoshinaga H. Risk factors for the development of non-insulin-dependent diabetes mellitus (NIDDM) in Japan. *Diabetes Res Clin Pract* 1994; **24**: S123–S127.

35 Iozzo P, Beck-Nielsen H, Laakso M, Smith U, Yki-Jarvinen H, Ferrannini E. Independent influence of age on basal insulin secretion in non-diabetic humans. European Group for the Study of Insulin Resistance. *J Clin Endocrinol Metab* 1999; **84**: 863–868.

36 Basu R, Breda E, Oberg AL, Powell CC, Dalla Man C, Basu A *et al.* Mechanism of the age-associated deterioration in glucose tolerance: contribution of alterations in insulin secretion, action, and clearance. *Diabetes* 2003; **52**: 1738–1748.

愛媛県南西部地区コホート研究

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研究要旨：愛媛県南西部地域における循環器疾患発症登録と同地域における約 4.5 千人の 10 年間に及ぶコホート研究から、当該地域全体の循環器疾患発症率の動向、ならびにウエスト周囲径と BMI レベルの循環器疾患発症に及ぼす影響について検討した。平成 11～19 年までの 9 年間をそれぞれ 3 年間毎の 3 期に分け、各期の年齢調整済み心筋梗塞・脳卒中発症率を男女別に算出したところ、男女とも心筋梗塞・脳卒中発症率は減少傾向であった。また、ウエスト周囲径と BMI に関して循環器疾患発症にかかる影響は現時点では小さかった。

A. 研究目的

地域における循環器疾患対策の評価指標として発症率の動向は非常に重要である。また、一般住民を対象としたコホート研究は、リスク評価として重要な研究ではあるが、その結果は、地域全体の動向と併せて対策へと結びつけていく必要がある。

本研究は、肥満関連指標の意義と循環器疾患リスクについて考察する。

B. 研究方法

本研究は、愛媛県南西部に位置する O 市（人口 50,774 人,平成 19 年）を対象集団として実施する、当地域においては、平成 11 年（1999 年）から地域の基幹病院を対象に、心筋梗塞と脳卒中の発症登録を実施してきた。平成 17 年 1 月から 19 年末までの循環器疾患発症登録調査を実施し、これまでのデータと併せ、心筋梗塞・脳卒中発症率の推移を検討した。心筋梗塞・脳卒中発症基準は、WHO モニカ基準に準じて、心筋梗塞は①定型的胸痛、②血清酵素、③心電図所見、④剖検所見、また、脳卒中は、「急激に神経症状が出現し、症状が 24 時間以上持続もしくは 24 時間以内に死亡したもの」とし、臨床症状として、①意識障害、②四肢麻痺、③感覚麻痺、④言語障害、⑤皮質症状（視力障害、失認・失行）、検査所見として①心電図、②剖検、③画像診断、等を把握した。

また、1996～1998 年に設定したコホート（5161 人）を 2007 年末まで追跡し、腹囲・BMI の脳卒中罹患に及ぼすハザード比を算出した。ハザード比は Cox 比例モデルに基づいて、P-spline 関数を使用し、非線形の検討を行った。統計解析には S-Plus 8.1J for Windows を用いた。

本研究計画は愛媛大学における医の倫理委員会による承認を受け、コホート研究に関しては書面による同意を得て実施している。

C. 研究結果

1. 地域脳卒中発症登録の結果

平成 11 年～平成 13 年を第 1 期、平成 14 年～平成 16 年を第 2 期、平成 17 年～平成 19 年を第 3 期とし、第 1 期を基準集団として、第 2 期、第 3 期の心筋梗塞、全脳卒中

の年齢調整発症率を求めた（図 1）。

脳卒中に比べて心筋梗塞の発症率は非常に低いことが特徴である。第 1 期から 3 期にかけて、心筋梗塞、脳卒中いずれも横ばい、もしくは減少していた。

2. コホート研究の結果

同域における脳卒中既往歴のない 40 歳以上の 4,536 人を 2007 年末まで追跡した。

ベースラインのウエスト周囲径と循環器疾患危険因子との関連を示した（表）。ウエスト周囲径が大きくなるに従って直線的にリスクは上昇した。ウエスト周囲径と BMI について、循環器疾患、心筋梗塞、脳卒中発症のハザード比を求めた（図 2）。BMI と心筋梗塞発症との間に有意な線形の関連を認めたが、ウエスト周囲径と循環器疾患発症との明らかな関連は認めなかった。

D. 考察

ウエスト周囲径が大きくなるに従って、明らかに血圧等の循環器疾患の危険因子の状況は悪くなった。しかしながら、ウエスト周囲径や BMI の増加は、循環器疾患発症リスクを上げているとは言い難い。このことは、肥満がリスクを上昇させて、結果として循環器疾患の発症リスクを増大させているということが、同地域では当てはまらないことを示唆している。

E. 結論

愛媛県南西部地域におけるコホート研究から、最近の循環器疾患発症にかかる肥満の影響について検討したところ、ウエスト周囲径と BMI レベルの影響は小さいことが示唆された。

F. 研究発表

1. 論文発表

1. Saito I, et al. Impact of weight change on specific-cause mortality among middle-aged Japanese individuals. J Epidemiol Community Health 2009; 63: 447-54.

2. Saito I, et al. Metabolic syndrome and all-cause and cardiovascular disease mortality: Japan Public Health Center-based Prospective (JPHC) Study. Circ J 2009; 73: 878-84.

3. Noda H, Iso H, Saito I, et al. The impact of the metabolic syndrome and its components on the incidence of ischemic heart disease and stroke: the Japan public health center-based study. Hypertens Res 2009; 32: 289-98.

2. 学会発表

1. 斉藤功，他．ウエスト周囲径レベルと循環器疾患発症との関連：大洲コホート研究．第 68 回日本公衆衛生学会総会（奈良），2009.

2. 森浩美，斉藤功，他．愛媛県大洲市における 9 年間の循環器疾患発症の推移．第 68 回日本公衆衛生学会総会（奈良），2009.

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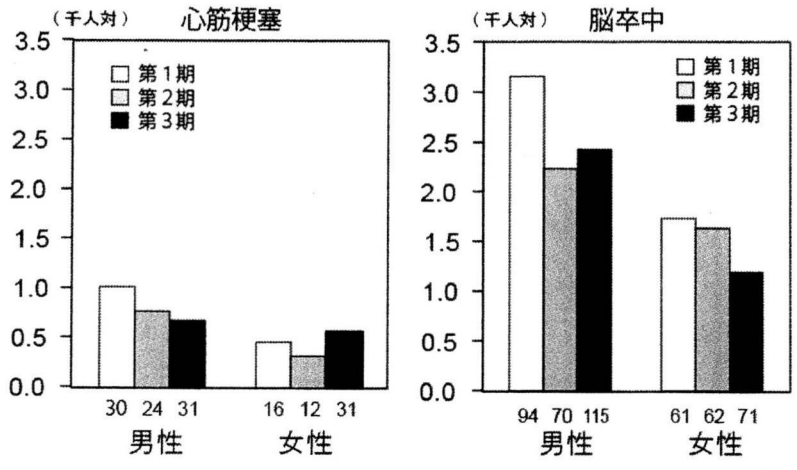

図1　心筋梗塞と脳卒中発症率の推移

表　ウエスト周囲径と循環器疾患危険因子

		ウエスト周囲径レベル				
		< 75cm	75-79	80-84	85-89	90+
男性	年齢	65.9	65.2	63.4	64.1	64.2
	最大血圧，mmHg	130.3	131.2	134.6	136.9	136.9
	最小血圧，mmHg	75.3	77.7	79.9	80.2	82.6
	総コレステロール,mg/dl	184.8	190.7	198.6	198.9	199.2
	HDL コレステロール,mg/dl	64.3	58.9	55.6	51.7	49.8
	中性脂肪,mg/dl（中央値）	75	95	114	127	136
	血糖値,mg/dl（中央値）	95	95	98	100	99
女性	年齢	60.8	60.9	62.7	63.2	64.7
	最大血圧，mmHg	127	129	131.9	134.1	136.9
	最小血圧，mmHg	73.7	74.8	76.2	78.5	79.5
	総コレステロール,mg/dl	208.3	215.1	216.8	222.3	220.5
	HDL コレステロール,mg/dl	65.9	62.8	59.2	57.8	55.5
	中性脂肪,mg/dl（中央値）	84	96.5	112	119	125.5
	血糖値,mg/dl（中央値）	93	96	97	97	98

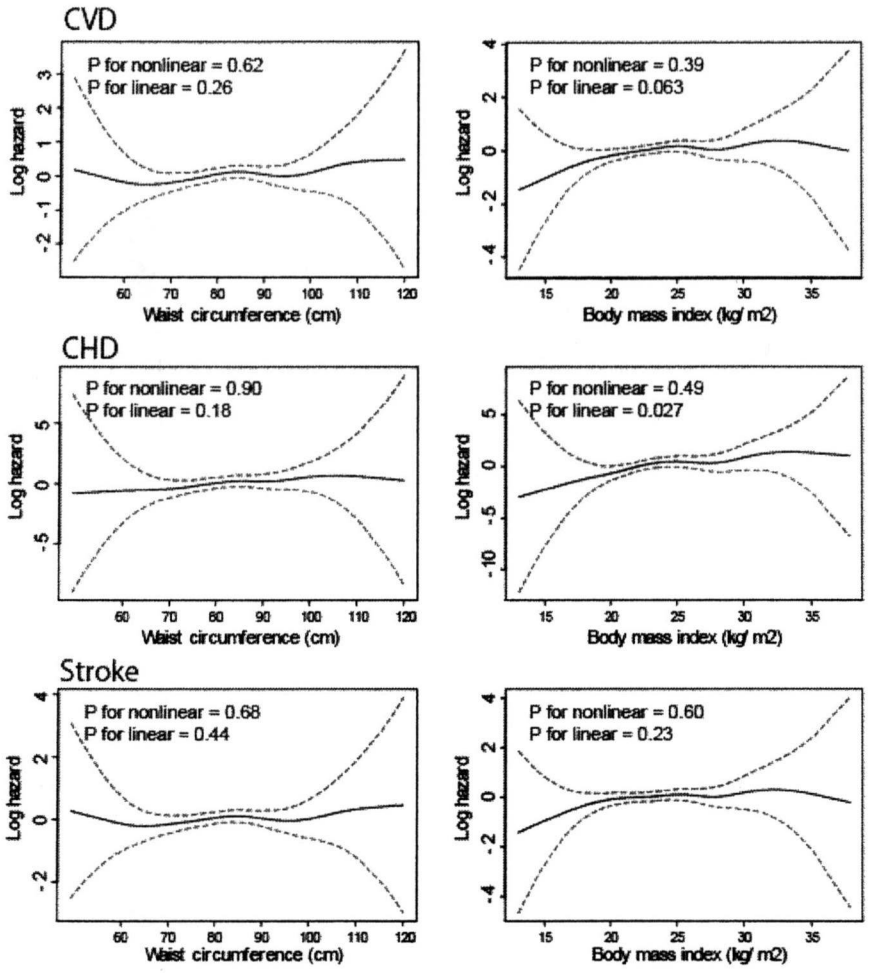

図2　本コホート研究におけるウエスト周囲径（左列）、並びにBMIレベル（右列）と全循環器疾患（CVD）、心筋梗塞（CHD）、脳卒中（Stroke）のハザードリスクとの関連。実線は年齢調整済み対数ハザード比、点線は95%信頼区間を示す。

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Metabolic Syndrome and All-Cause and Cardiovascular Disease Mortality

—— Japan Public Health Center-Based Prospective (JPHC) Study ——

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Background: Although the metabolic syndrome (MetS) is considered to be caused primarily by visceral fat accumulation, epidemiological evidence is lacking as to whether or not obesity is an essential element in the syndrome.

Methods and Results: Between 1990 and 2005, the Japan Public Health Center-based Prospective (JPHC) Study conducted baseline measurements of metabolic risk factors in 12,412 men and 21,639 women, aged 40–69 years, with no history of cardiovascular disease (CVD) or cancer. To clarify the role of obesity, which the definition of MetS in Japan has adopted as an essential criterion, clustering of risk factors in data grouped according to overweight condition was examined. During a 12.3-year follow-up there were 2,040 deaths, including 947 from cancers and 304 from CVD. MetS significantly increased the hazard ratios for all-cause mortality in women and CVD mortality in men. Non-overweight with ≥2 risk factors had a similar impact on all-cause and CVD mortality. Clustering of metabolic factors caused a linear increase in the hazard ratios for mortality.

Conclusions: MetS caused moderate increases in all-cause and CVD mortality. However, the MetS definition requiring obesity may not necessarily identify non-overweight individuals who have a high mortality risk and are more prevalent than subjects with MetS. (*Circ J* 2009; **73:** 878–884)

Key Words: Cardiovascular disease; Cohort study; Epidemiology; Metabolic syndrome; Mortality

The metabolic syndrome (MetS) is considered to have an impact on atherosclerosis development and mortality from all-cause and cardiovascular disease (CVD)[1–3] The syndrome is caused primarily by visceral fat accumulation, which activates several cytokines produced by adipose tissue[4] The International Diabetes Federation (IDF) definition of MetS requires the presence of central obesity plus 2 of the following factors: raised level of fasting plasma triglycerides or glucose, increased blood pressure (BP) or reduced level of plasma high-density lipoprotein-cholesterol[5] The Japanese definition also uses different criteria for waist circumference: ≥85 cm for men and ≥90 cm for women[6]

A Korean study has shown that the IDF definition of MetS is inferior to the definition of the Third Report of the US National Cholesterol Education Program, Adult Treatment Panel III (ATP III) for detecting subjects at high risk of developing CVD[7] Recently, a European population based study also demonstrated that the IDF definition may not detect non-obese individuals with a high risk of CVD mortality, because of the increased risk in individuals with clustering of risk factors, regardless of the presence or absence of central obesity[8] These findings raise the question as to whether or not definitions, such as the IDF and the Japanese, that have central obesity as a criterion are adequate for detecting individuals with a high CVD risk.

To better understand the impact of MetS and the clustering of risk factors on mortality we conducted a long-term prospective study of 34,051 Japanese men and women.

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Conflict of interest: none.

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Methods

Study Population

The subjects were 12,412 men and 21,639 women, aged 40–69 years, who took part in the Japan Public Health Center-based Prospective (JPHC) Study. For inclusion in the study, subjects could not have a history of ischemic heart disease (IHD), stroke or cancer and had to be available for health checkups of metabolic risk factors. The JPHC Study consisted of Cohorts I and II, which began in 1990 and 1993, respectively, as described elsewhere[9] Briefly, Cohort I was drawn from residents aged 40–59 years in 5 public health center (PHC) areas (Ninohe PHC of Iwate Prefecture, Yokote PHC of Akita Prefecture, Saku PHC of Nagano Pre-

Table 1. Baseline Characteristics of Men and Women Grouped According to the Presence or Absence of the Japanese Definition of the MetS

	MetS (Japan)			
	Men		Women	
	Presence	Absence	Presence	Absence
n	1,756	10,656	2,008	19,631
Age, years	53.5	53.8	56.1	52.9
Body mass index, kg/m^2	27.3	22.9	27.9	23.1
Systolic BP, mmHg	142.4	129.5	143.3	126.4
Diastolic BP, mmHg	86.4	78.8	83.9	75.5
Total cholesterol, mmol/L	5.36	5.04	5.74	5.36
HDL-cholesterol, mmol/L	1.17	1.43	1.26	1.54
Triglycerides (median), mmol/L	2.14	1.14	2.02	1.01
Fasting glucose (median), mmol/L	6.1	5.3	5.9	5.1
Smoking status				
Non-smoker, %	62.5	54.1	95.6	94.4
1–19 cigarettes/day, %	15.1	21.1	3.2	4.5
≥20 cigarettes/day, %	22.3	24.8	1.3	1.1
Alcohol consumption, g/week	218.9	194.0	9.8	12.7
Sports and physical exercise, % ≥1 day/week	20.2	20.5	22.0	21.9
Persons taking drugs for, %				
Hypertension	40.6	20.8	54.8	23.6
Hyperlipidemia	7.7	2.3	16.7	4.3
Diabetes	6.3	2.6	7.3	1.6
Gout	5.8	2.8	0.8	0.6
Persons diagnosed by a doctor, %				
Hypertension	52.8	27.2	62.1	31.8
Diabetes	15.1	8.9	12.5	4.0
Liver disease	4.5	4.1	1.1	2.1
Kidney disease	3.5	3.7	4.1	4.4

MetS, metabolic syndrome; BP, blood pressure; HDL, high-density lipoprotein.

fecture, Chubu PHC of Okinawa Prefecture, and Katsushika PHC of Tokyo), and Cohort II was drawn from residents aged 40–69 years in 6 areas (Mito PHC of Ibaraki Prefecture, Nagaoka PHC of Niigata Prefecture, Suita PHC of Osaka Prefecture, Chuo-higashi PHC of Kochi Prefecture, Kamigoto PHC of Nagasaki Prefecture and Miyako PHC of Okinawa Prefecture). The Cohort I data included 2,754 men and 4,940 women who were revisited in 1995 because their metabolic risk factors had not been measured at the first examination in 1990. The study was approved by the Ethical Committee of the National Cancer Center.

Measurements

Trained technicians measured BP using standard mercury sphygmomanometers. Body mass index (BMI, kg/m^2) was calculated as weight divided by the square of height in meters. Serum levels of total cholesterol, high-density lipoprotein-cholesterol (HDL-C) and triglycerides were measured in accredited laboratories with quality control certification from the Osaka Medical Center for Health Science and Promotion, a member of the Cholesterol Reference Method Laboratory Network (CRMLN).[10] The fasting condition for blood collection was defined as ≥8 h since the last meal. A self-administered questionnaire was conducted at baseline to assess medical history, smoking habit and regular alcohol consumption. The amount of ethanol per week was evaluated by measuring the weekly frequency of drinking and the typical dose of alcoholic beverage (beer, sake, whiskey, shochu or wine). A history of hypertension or diabetes was ascertained by the question, "Have the following conditions been diagnosed by physicians?" with hypertension, diabetes and other chronic diseases being listed as potential responses.

MetS was defined using both the modified Japanese criteria[6] and the National Cholesterol Education Program, ATP III[1] definition. Although both definitions require central obesity as defined by waist circumference, we used BMI values as we did not measure waist circumference in our study. The MetS of Japan definition includes waist circumference ≥85 cm in men and ≥90 cm in women as essential elements in the adapted IDF definition, corresponding to a BMI ≥25 kg/m^2.[11] Therefore, in the present study, MetS was defined as a BMI ≥25 kg/m^2 plus any 2 of the following factors: (1) dyslipidemia (high triglycerides [≥1.69 mmol/L, 150 mg/dl], and/or low HDL-C [<1.03 mmol/L, 40 mg/dl], and/or medication use), (2) raised BP (systolic BP ≥130 mmHg, diastolic BP ≥85 mmHg, and/or medication use), (3) raised plasma glucose (≥6.1 mmol/L (110 mg/dl) fasting, or ≥7.8 mmol/L (140 mg/dl) non-fasting, and/or medication use). The ATP III definition defines subjects with MetS having 3 or more of the following factors: (1) raised plasma glucose (≥5.6 mmol/L (100 mg/dl) fasting, or ≥7.8 mmol/L (140 mg/dl) non-fasting, and/or medication use), (2) raised BP, (3) high triglycerides, (4) low HDL-C <1.03 mmol/L (40 mg/dl) in men and <1.29 mmol/L (50 mg/dl) in women, and (5) BMI ≥25 kg/m^2. The values of raised BP and high triglycerides were the same as those used in the Japanese MetS definition.

Until 1995, the underlying cause of death was determined based on death certificates coded according to the criteria of the International Classification of Diseases, ninth revision (ICD-9). From 1995 onwards, the codes were translated into the corresponding ICD-10 codes. Deaths from cancer, IHD and stroke were defined as C00–97, I20–25 and I60–69 (ICD-10), respectively, with IHD and stroke combined as CVD in the analyses.

Statistical Analysis

The median period of follow-up was 12.3 years from

Table 2. Multivariate Adjusted HRs and 95% CI for the ATP III and Japanese Definitions of the MetS and Determinants for Specific Causes of Death in Men Aged 40–69 in the JPHC Study

	Model*	Underlying cause of death				
		All-cause	Cancer	IHD	Stroke	CVD
No. of deaths		1,240	573	71	106	177
MetS (Japan)	Model 1	1.04 (0.88–1.22)	0.98 (0.77–1.26)	2.17 (1.27–3.72)	1.48 (0.90–2.43)	1.74 (1.21–2.51)
	Model 2	1.07 (0.90–1.27)	1.06 (0.82–1.36)	1.91 (1.05–3.48)	1.31 (0.75–2.29)	1.54 (1.02–2.31)
ATP III MetS	Model 1	1.07 (0.94–1.23)	0.95 (0.77–1.17)	1.98 (1.21–3.25)	1.38 (0.89–2.14)	1.61 (1.16–2.23)
	Model 2	1.06 (0.92–1.23)	0.97 (0.78–1.20)	1.76 (1.03–3.01)	1.20 (0.74–1.94)	1.41 (0.99–2.02)
MetS elements						
Overweight	Model 1	0.86 (0.76–0.99)	0.92 (0.76–1.12)	1.88 (1.16–3.04)	0.93 (0.60–1.46)	1.27 (0.92–1.75)
	Model 2	0.92 (0.80–1.06)	1.02 (0.83–1.24)	1.98 (1.18–3.32)	0.76 (0.45–1.26)	1.16 (0.82–1.66)
Raised BP	Model 1	1.16 (1.03–1.32)	1.03 (0.86–1.23)	1.49 (0.87–2.55)	2.03 (1.25–3.30)	1.78 (1.24–2.54)
	Model 2	1.19 (1.04–1.35)	1.04 (0.87–1.25)	1.53 (0.87–2.70)	2.29 (1.35–3.87)	1.90 (1.30–2.79)
Dyslipidemia	Model 1	1.13 (1.01–1.28)	1.08 (0.90–1.29)	2.32 (1.44–3.73)	1.12 (0.75–1.69)	1.52 (1.12–2.05)
	Model 2	1.10 (0.97–1.24)	1.07 (0.89–1.28)	2.11 (1.27–3.49)	1.01 (0.66–1.56)	1.27 (0.91–1.77)
Raised plasma glucose	Model 1	1.19 (1.04–1.37)	1.04 (0.83–1.29)	1.96 (1.17–3.28)	1.45 (0.93–2.27)	1.64 (1.17–2.30)
	Model 2	1.22 (1.05–1.41)	1.07 (0.86–1.33)	1.92 (1.10–3.35)	1.27 (0.77–2.08)	1.51 (1.04–2.18)

*Model 1 was adjusted for the JPHC communities and age. Model 2 was further adjusted for fasting conditions at blood collection, smoking status (non-smoker, 1–19 cigarettes/day, and ≥20 cigarettes/day), alcohol consumption (g/week) and sports and physical exercise.
HRs, hazard ratios; CI, confidence interval; ATP III, National Cholesterol Educational Program, Adult Treatment Panel III in the US; JPHC, the Japan Public Health Center-based Prospective; IHD, ischemic heart disease; CVD, cardiovascular disease.

Table 3. Multivariate Adjusted HRs and 95% CI for the ATP III and Japanese Definitions of the MetS and Determinants for Specific Causes of Death in Women Aged 40–69 in the JPHC Study

	Model*	Underlying cause of death				
		All-cause	Cancer	IHD	Stroke	CVD
No. of deaths		800	374	38	89	127
MetS (Japan)	Model 1	1.25 (1.02–1.54)	1.26 (0.93–1.70)	2.52 (1.18–5.38)	0.86 (0.43–1.72)	1.28 (0.77–2.12)
	Model 2	1.24 (1.00–1.53)	1.27 (0.94–1.73)	2.56 (1.19–5.48)	0.88 (0.44–1.77)	1.31 (0.79–2.18)
ATP III MetS	Model 1	1.23 (1.05–1.44)	1.18 (0.93–1.50)	2.08 (1.07–4.01)	1.24 (0.77–1.98)	1.46 (1.00–2.13)
	Model 2	1.22 (1.03–1.43)	1.17 (0.92–1.49)	1.90 (0.97–3.74)	1.26 (0.79–2.03)	1.44 (0.98–2.11)
MetS elements						
Overweight	Model 1	0.99 (0.85–1.15)	1.07 (0.86–1.33)	1.97 (1.03–3.76)	1.03 (0.66–1.61)	1.26 (0.88–1.81)
	Model 2	0.99 (0.85–1.15)	1.07 (0.85–1.33)	2.03 (1.05–3.90)	1.07 (0.68–1.67)	1.30 (0.90–1.88)
Raised BP	Model 1	1.22 (1.05–1.42)	0.97 (0.78–1.21)	1.17 (0.58–2.35)	1.81 (1.10–2.97)	1.57 (1.05–2.36)
	Model 2	1.24 (1.06–1.44)	1.00 (0.83–1.25)	1.16 (0.55–2.26)	1.81 (1.10–2.98)	1.55 (1.03–2.33)
Dyslipidemia	Model 1	1.05 (0.90–1.23)	1.13 (0.90–1.42)	2.21 (1.15–4.23)	1.00 (0.62–1.60)	1.29 (0.88–1.88)
	Model 2	1.03 (0.87–1.21)	1.09 (0.87–1.38)	2.08 (1.06–4.05)	1.02 (0.63–1.64)	1.17 (0.79–1.73)
Raised plasma glucose	Model 1	1.70 (1.40–2.06)	1.33 (0.97–1.82)	2.76 (1.29–5.93)	1.23 (0.65–2.34)	1.64 (1.01–2.66)
	Model 2	1.70 (1.39–2.07)	1.42 (1.03–1.94)	2.80 (1.29–6.07)	1.23 (0.65–2.35)	1.64 (1.01–2.68)

*See footnote of Table 2. See Tables 1,2 for abbreviations.

either 1990 or 1995 (Cohort I) or 1993 (Cohort II) to the end of 2005. The person-years studied were calculated as the period from baseline to either the first endpoint (death, emigration) or December 31, 2005.

Cox proportional hazard models were used to calculate sex-specific hazard ratios (HR) and 95% confidence intervals (CI) after adjustment for age (continuous), JPHC communities (dummy variables) and fasting condition, smoking status (non-smoker, 1–19 cigarettes/day, or ≥20 cigarettes/day), alcohol consumption and sports and physical exercise (≥1 day/week, other). The risk estimations of all-cause and CVD mortality were calculated on data grouped according to the different MetS definitions, overweight category (BMI ≥25 kg/m^2 or <25 kg/m^2) or number of metabolic risk factors. A category-specific population attributable fraction (PAF) was computed as pd×(HR−1)/HR, where pd is the proportion of cases falling into the category and HR is the hazard ratio for that category.[12] Statistical significance was assumed at $P<0.05$. SAS software, version 9.1 (SAS Institute, Inc, Cary, NC, USA) was used for all the analyses.

Results

The median follow up period was 12.3 years, during which we documented 2,040 deaths in the 12,412 men and 21,639 women of the combined Cohorts I and II, including 947 cancer and 304 CVD deaths. **Table 1** shows sex-specific population profiles according to the MetS criteria in Japan. The percentage of subjects aged 40–69 years classified as having the MetS was 14.1% in men and 9.3% in women. In the present study, the percentages of subjects with components of the MetS, including overweight, raised BP, dyslipidemia, and raised plasma glucose, were 29.2%, 59.0%, 36.7% and 16.6% in men and 29.7%, 50.6%, 24.4% and 8.0% in women, respectively.

Tables 2 and **3** list the multivariable adjusted HRs for the various MetS definitions and determinants for mortality from all-causes, cancer, IHD, stroke or CVD in men and women. In men, neither the MetS of Japan nor the ATP III MetS definition increased all-cause mortality risk. However, both classifications increased IHD and CVD mortality. For example, the HR for CVD mortality using the MetS criteria of Japan was 1.54 (95%CI, 1.02–2.31) in model 2. There

Table 4. Multivariate Adjusted HRs and 95% CIs for All-Cause and CVD Mortality According to the Number of Risk Factors and the Combination of Overweight and Other Risk Factors in Men

Categories	Population	All-cause			CVD		
		No. of deaths	Model*		No. of deaths	Model*	
			Model 1	Model 2		Model 1	Model 2
No. of risk factors**							
0	2,633	207	1.00	1.00	21	1.00	1.00
1	4,411	478	1.16 (0.98–1.36)	1.16 (0.98–1.38)	54	1.26 (0.76–2.09)	1.32 (0.79–2.22)
2	3,247	341	1.16 (0.97–1.38)	1.19 (0.99–1.43)	58	1.91 (1.16–3.15)	1.94 (1.16–3.26)
3	1,710	169	1.16 (0.95–1.42)	1.19 (0.96–1.47)	32	2.12 (1.22–3.68)	1.83 (1.01–3.32)
4	381	45	1.51 (1.10–2.09)	1.61 (1.15–2.25)	12	3.93 (1.93–8.01)	3.84 (1.79–8.27)
P for trend			0.041	0.017		<0.001	<0.001
Combination of overweight and 3 other risk factors							
Non-overweight and 0 risk factors	2,663	207	1.00	1.00	21	1.00	1.00
Non-overweight and 1 risk factor	3,923	461	1.23 (1.04–1.45)	1.22 (1.03–1.45)	53	1.36 (0.82–2.27)	1.42 (0.84–2.38)
Non-overweight and ≥2 risk factors	2,201	281	1.28 (1.07–1.54)	1.28 (1.06–1.54)	48	2.13 (1.27–3.58)	2.12 (1.24–3.63)
Overweight and 0–1 risk factors	1,869	124	0.86 (0.69–1.08)	0.94 (0.75–1.19)	18	1.21 (0.64–2.28)	1.21 (0.61–2.36)
Overweight and ≥2 risk factors	1,756	167	1.17 (0.96–1.44)	1.22 (0.99–1.52)	37	2.51 (1.46–4.29)	2.24 (1.26–3.98)

*See the footnote of Table 2. **Indicates the 4 elements of overweight, raised BP, dyslipidemia and raised plasma glucose.
See Table 2 for abbreviations.

Table 5. Multivariate Adjusted HRs and 95% CIs for All-Cause and CVD Mortality According to the Number of Risk Factors and the Combination of Overweight and Other Risk Factors in Women

Categories	Population	All-cause			CVD		
		No. of deaths	Model*		No. of deaths	Model*	
			Model 1	Model 2		Model 1	Model 2
No. of risk factors**							
0	6,938	171	1.00	1.00	19	1.00	1.00
1	7,502	285	1.10 (0.90–1.33)	1.07 (0.88–1.31)	43	1.33 (0.77–2.29)	1.27 (0.73–2.21)
2	4,973	211	1.10 (0.89–1.35)	1.08 (0.88–1.34)	40	1.66 (0.95–2.90)	1.62 (0.93–2.84)
3 (≥3 for CVD)	1,965	110	1.41 (1.10–1.80)	1.37 (1.07–1.77)	25	2.27 (1.23–4.19)	2.27 (1.23–4.20)
4	261	23	2.02 (1.30–3.14)	2.04 (1.31–3.17)	–	–	–
P for trend			0.002	0.003		0.005	0.005
Combination of overweight and 3 other risk factors							
Non-overweight and 0 risk factors	6,938	171	1.00	1.00	19	1.00	1.00
Non-overweight and 1 risk factor	6,022	248	1.14 (0.93–1.39)	1.12 (0.91–1.37)	38	1.36 (0.78–2.37)	1.30 (0.74–2.28)
Non-overweight and ≥2 risk factors	2,248	125	1.33 (1.05–1.69)	1.30 (1.02–1.66)	23	1.88 (1.01–3.50)	1.81 (0.96–3.39)
Overweight and 0–1 risk factors	4,423	146	0.98 (0.78–1.23)	0.97 (0.77–1.22)	29	1.63 (0.91–2.93)	1.63 (0.91–2.92)
Overweight and ≥2 risk factors	2,008	110	1.38 (1.08–1.77)	1.34 (1.04–1.73)	18	1.83 (0.95–3.54)	1.84 (0.95–3.55)

*See the footnote of Table 2. **Indicates the 4 elements of overweight, raised BP, dyslipidemia and raised plasma glucose.
See Table 2 for abbreviations.

was no relationship between cancer mortality and the MetS or any of its determinants, whereas raised BP and increased plasma glucose were significant predictors of all-cause mortality after adjustment for potential confounders. Raised BP and plasma glucose levels were also both significant risk factors for CVD deaths, whereas being overweight, hypertensive or dyslipidemic doubled the risk of IHD mortality.

As shown in **Table 3**, multivariable adjusted HRs for all-cause mortality in women were increased for both the MetS classifications of Japan and ATP III. The Japanese MetS criteria also predicted IHD mortality, but not CVD mortality when combined with stroke. Women with high BP and raised plasma glucose levels had greater risk of all-cause mortality. We found a close association between IHD mortality and subjects who were overweight and dyslipidemic with a raised plasma glucose level. In contrast, the risk of stroke mortality was increased by raised BP only. Raised BP and increased plasma glucose levels were also significant predictors for CVD mortality.

Multivariable adjusted HRs for all cause and CVD mortality are shown for men (**Table 4**) and women (**Table 5**), grouped according to the number of metabolic risk factors present and body weight range. In men, there was a linear relationship between the HRs for all-cause and CVD mortality and an increase in the number of risk factors. Stratification of the data according to the overweight category showed men who were not overweight with 1 or ≥2 risk factors had a higher risk for all-cause mortality than overweight men with the same number of factors. Regarding CVD death, men with ≥2 risk factors, were at approximately 2-fold greater risk than men with no risk factors, regardless of whether or not they were overweight. The calculations of PAF in non-overweight and overweight men with ≥2 risks factors were 9.4% and 7.8%, respectively.

Similar analyses in women showed the HRs for all-cause and CVD mortality both increased in a linear manner. Multivariable adjusted HRs for all-cause mortality in non-overweight and overweight women with ≥2 risk factors were almost the same. Significant increases in HRs were not seen in model 2, although overweight and non-overweight women with ≥2 risk factors were likely to have a relatively higher risk of CVD mortality.

Figure shows the multivariable adjusted HRs for CVD mortality for the combination of raised BP, increased plasma

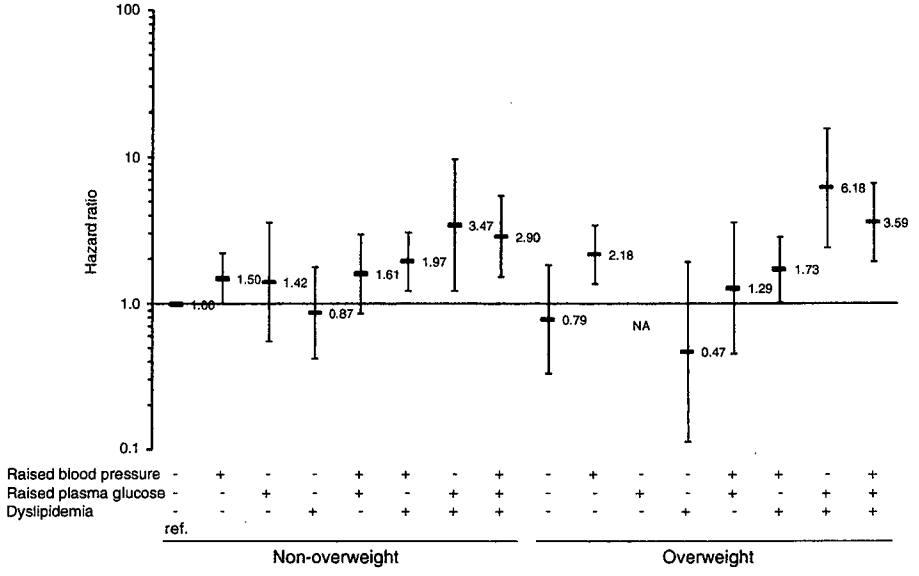

Figure. Multivariate adjusted hazard ratios for cardiovascular disease mortality of clustering of metabolic components in the combined data of men and women, grouped according to overweight category. The hazard ratios were calculated using subjects who were not overweight with no risks as the reference group.

glucose and dyslipidemia stratified according to the overweight category ranges in the combined data of men and women. The HRs increased significantly in subjects who had raised BP alone or those who had raised BP and/or raised plasma glucose combined with dyslipidemia, regardless of being overweight or not.

Discussion

This large prospective study confirmed that MetS has a moderate impact on all-cause and CVD mortality. We found the HRs for both types of mortality were increased not only in individuals with MetS, but also in non-overweight individuals with a constellation of risk factors compared with non-overweight individuals with no risk factors. Mortality risk increased in a linear manner according to the number of MetS factors present, including being overweight. We therefore do not agree with the recent proposal that the presence of the MetS identifies all individuals with a high risk of CVD mortality.

The prevalence of MetS in the present study was 14.1% in men and 9.3% in women aged 40–69 years. These percentages are almost similar to those reported in other investigations in which BMI was adopted for the MetS definition[13,14] The Japan National Health and Nutrition Survey documented the prevalence using waist measurements and showed 22.8% of men and 8.7% of women had MetS[15]

Various committees have proposed criteria for the IDF and Japanese definitions of MetS, both of which require central obesity plus any 2 of the metabolic risk factors[5] A small number of studies have reported that the ATP III definition of MetS clearly predicted stroke occurrence in the Japanese population;[16] whereas the Japanese classification did not[17] The recent concept requiring central obesity as an essential component was seemingly based on the pathogenesis of MetS[4,18] However, to date this requirement has not been supported by epidemiological evidence at the population level. With regard to detecting those at high risk, a European study was critical of the IDF definition because the criteria did not identify high-risk individuals[8]

Not surprisingly, it has been reported that the association between obesity and mortality is very weak in Japanese subjects[19] Instead, high mortality rates from all-cause and CVD deaths were found in individuals with lower BMI or weight loss since age 20, with inverse, L-shaped or U-shaped associations being observed between these variables[20] Although our study did not assess central obesity by measuring waist circumference, being overweight did not have a major role in identifying individuals at high risk of all-cause and CVD mortality.

The main finding of our study was that in the general Japanese population there were more non-overweight individuals with a constellation of risk factors than overweight individuals with the same constellation, with both groups having a similar mortality risk. When waist circumference was assessed, these unbalanced proportions for Japanese were confirmed;[17] and were quite different from proportions seen in a European population[8] Because of this, the PAF was greater in non-overweight individuals with 2 or more risk factors than in overweight individuals with the same number of risk factors. This finding suggests that strategies for preventing CVD may not be sufficient in people with MetS.

Hypertension and diabetes are strong predictors of all-cause and CVD mortality in the Japanese population. Prospective studies in Japan report that elevated plasma glucose is a major contributor to CVD mortality[21] and that non-obese participants with clustering of risk factors are at increased mortality risk regardless of obesity[13] Those results are in general agreement with our findings. Furthermore, it has been documented that HRs of incident stroke in Japan are nearly the same between non-central and centrally obese individuals with 1 and ≥2 metabolic components[17] Our data also demonstrated that people with all the components of

Mets did not have increased HRs for CVD mortality, and regardless of them being overweight, this ratio was lower than in people with the 2 MetS components of raised plasma glucose and dyslipidemia. Although we are unable to explain the reason for this finding, a possible explanation may be that individuals with more serious conditions tend to need medication and were therefore excluded from participating in this study. Alternatively, smoking is a well-established risk factor for CVD mortality. In the present study, detailed analysis of data stratified by smoking habits was carried out and verified that metabolic risks had a similar effect on all-cause and CVD mortality in both smokers and non-smokers.

Although the JPHC study has the major advantages of including several large cohorts throughout Japan and the rich variability in health practices among these regions, several limitations of the study need to be taken into account. Firstly, we did not measure waist circumference. Several studies in Japan have used BMI values in the MetS definition, with Japanese guidelines recommending a BMI $\geq 25\,kg/m^2$ as representing obesity![1] This value corresponds to a cut-off point for visceral fat area of $100\,cm^2$, regarded as the gold standard for defining central obesity. Correlation coefficients of visceral fat area with BMI were reported to be 0.61 in men and 0.63 in women[11] values that were almost equal to the correlations we observed with waist circumference. Secondly, fasting blood samples were collected from only 54% of the subjects. Although we used different cut-off points for fasting and non-fasting plasma glucose levels, it is possible misclassification of the MetS may have occurred because we used non-fasting blood samples. The prevalence of the MetS in fasting and non-fasting subjects was 13.1% and 15.5% in men and 6.6% and 11.8% in women, respectively. People who had blood samples taken in the non-fasting state were more likely to have dyslipidemia and to be taking antihypertensive medication. Thirdly, although clustering of risk factors was not a significant predictor for CVD mortality in non-overweight and overweight women, this relationship nearly reached statistical significance ($P< 0.1$). Because of the smaller number of CVD deaths in women, it is likely beta errors were relatively high. Finally, subjects in the study were selected if they had undergone a health checkup and were therefore not randomly recruited from the general population. A previous study in this cohort showed mortality was relatively low compared with that in the general population[22] This may limit extrapolation of our findings to the general population.

In conclusion, although our study has several limitations, such as not assessing waist circumference, we showed that the presence of MetS increased all-cause and CVD mortality. We also showed that MetS definitions requiring obesity as an essential criterion certainly overlook non-overweight high risk individuals who have a high mortality risk and, in the present study, were greater in number than subjects with MetS. Indeed, a further large prospective study is needed to clarify the association of central obesity and MetS with CVD mortality in the Japanese population.

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References

1. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005; **112:** 2735–2752.
2. Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 2002; **288:** 2709–2716.
3. Dekker JM, Girman C, Rhodes T, Nijpels G, Stehouwer CD, Bouter LM, et al. Metabolic syndrome and 10-year cardiovascular disease risk in the Hoorn Study. *Circulation* 2005; **112:** 666–673.
4. Matsuzawa Y, Funahashi T, Kihara S, Shimomura I. Adiponectin and metabolic syndrome. *Arterioscler Thromb Vasc Biol* 2004; **24:** 29–33.
5. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome: A new worldwide definition: A Consensus Statement from the International Diabetes Federation. *Diabet Med* 2006; **23:** 469–480.
6. Committee to Evaluate Diagnostic Standards for Metabolic Syndrome. Definition and the diagnostic standard for metabolic syndrome. *Nippon Naika Gakkai Zasshi* 2005; **94:** 794–809 (in Japanese).
7. Kim HM, Kim DJ, Jung IH, Park C, Park J. Prevalence of the metabolic syndrome among Korean adults using the new International Diabetes Federation definition and the new abdominal obesity criteria for the Korean people. *Diabetes Res Clin Pract* 2007; **77:** 99–106.
8. Gao W. Does the constellation of risk factors with and without abdominal adiposity associate with different cardiovascular mortality risk? *Int J Obes (Lond)* 2008; **32:** 757–762.
9. Watanabe S, Tsugane S, Sobue T, Konishi M, Baba S. Study design and organization of the JPHC study: Japan Public Health Center-based Prospective Study on Cancer and Cardiovascular Diseases. *J Epidemiol* 2001; **11**(Suppl): S3–S7.
10. Nakamura M, Sato S, Shimamoto T. Improvement in Japanese clinical laboratory measurements of total cholesterol and HDL-cholesterol by the US Cholesterol Reference Method Laboratory Network. *J Atheroscler Thromb* 2003; **10:** 145–153.
11. Examination Committee of Criteria for 'Obesity Disease' in Japan. New criteria for 'obesity disease' in Japan. *Circ J* 2002; **66:** 987–992.
12. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health* 1998; **88:** 15–19.
13. Kadota A, Hozawa A, Okamura T, Kadowak T, Nakmaura K, Murakami Y, et al. Relationship between metabolic risk factor clustering and cardiovascular mortality stratified by high blood glucose and obesity: NIPPON DATA90, 1990–2000. *Diabetes Care* 2007; **30:** 1533–1538.
14. Hsieh SD, Muto T. Metabolic syndrome in Japanese men and women with special reference to the anthropometric criteria for the assessment of obesity: Proposal to use the waist-to-height ratio. *Prev Med* 2006; **42:** 135–139.
15. Nishimura R, Nakagami T, Tominaga M, Yoshiike N, Tajima N. Prevalence of metabolic syndrome and optimal waist circumference cut-off values in Japan. *Diabetes Res Clin Pract* 2007; **78:** 77–84.
16. Iso H, Sato S, Kitamura A, Imano H, Kiyama M, Yamagishi K, et al. Metabolic syndrome and the risk of ischemic heart disease and stroke among Japanese men and women. *Stroke* 2007; **38:** 1744–1751.
17. Saito I, Konishi M, Watanabe K, Kondo H, Fujimotos K, Okada K. The metabolic syndrome and risk of stroke in a rural community in Japan. *Nippon Koshu Eisei Zasshi* 2007; **54:** 677–683 (in Japanese).
18. Reaven GM. Role of insulin resistance in human disease [Banting lecture 1988]. *Diabetes* 1988; **37:** 1595–1607.
19. Tsugane S, Sasaki S, Tsubono Y. Under- and overweight impact on mortality among middle-aged Japanese men and women: A 10-y follow-up of JPHC study cohort I. *Int J Obes Relat Metab Disord* 2002; **26:** 529–537.
20. Chei CL, Iso H, Yamagishi K, Inoue M, Tsugane S. Body mass index and weight change since 20 years of age and risk of coronary heart disease among Japanese: The Japan Public Health Center-Based Study. *Int J Obes (Lond)* 2008; **32:** 144–151.
21. Kadowaki S, Okamura T, Hozawa A, Kadowaki T, Kadota A, Murakami Y, et al. Relationship of elevated casual blood glucose level with coronary heart disease, cardiovascular disease and all-cause mortality in a representative sample of the Japanese population: NIPPON DATA80. *Diabetologia* 2008; **51:** 575–582.
22. Iwasaki M, Yamamoto S, Otani T, Inoue M, Hanaoka T, Sobue T, et al. Generalizability of relative risk estimates from a well-defined population to a general population. *Eur J Epidemiol* 2006; **21:** 253–262.

Appendix 1

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Impact of weight change on specific-cause mortality among middle-aged Japanese individuals

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ABSTRACT

Background: The aim of this study was to investigate the associations between long-term weight change after age 20 and overall mortality and cause-specific mortality in the general Asian population.

Methods: From 1990 to 2005, the Japan Public Health Center (JPHC)-based prospective study conducted a follow-up of 42 242 men and 46 177 women aged 40–69 years with no history of cardiovascular disease (CVD) or cancer. Sex-specific multivariable-adjusted hazard ratios for cause-specific mortality were computed in accordance with weight change categories from age 20, as assessed by a self-administered questionnaire, and clustered by the JPHC communities and age groups, using Cox's proportional hazard model.

Results: During the 12.9-year follow-up, there were 6494 deaths, including 2888 from cancer, 1011 from CVD and 2595 from other causes. In all, weight loss ≥5 kg since age 20 increased hazard ratios for all-cause mortality in men (1.44, 95% CI 1.32 to 1.56) and women (1.33, 95% CI 1.17 to 1.52) compared with maintenance of a stable weight, and elevated risk was also found within each age group. The risk of weight loss was higher for individuals in the younger age group. Weight loss predicted cancer and CVD mortality only for men ≥50 years of age. The increased risk was observed regardless of whether the individual was ill, a smoker or overweight at baseline or at age 20. There was an inverse association between weight gain and mortality risk.

Conclusion: Weight loss strongly predicted all-cause, cancer and CVD mortality, primarily for men. An unfavourable effect of weight gain was small at the population level.

Weight change and weight fluctuation are strongly associated with all-cause and cause-specific mortality. The Nurses' Health Study cohort found that obesity and weight gain since early adulthood were closely related to mortality from all causes.[1] Several US and European prospective studies documented an increased risk of mortality associated with weight loss[2–5] and weight fluctuation[6 7] in elderly or middle-aged people. However, it is controversial whether or not weight gain is more hazardous for life expectancy considering covariates related to body weight such as smoking and illness.[4 5] Recently, health policy has given much attention to obesity and weight gain linked to the metabolic syndrome.[8–10] However, relatively little is known about possible associations between long-term weight changes, especially weight loss, and mortality in the general Asian population.

A national survey in Japan documented that mean body mass index (BMI) was 23.2 kg/m^2 in men and 22.5 kg/m^2 in women aged 15 years or over, and the percentages of obesity (≥30.0 kg/m^2) in men and women were very low: 2.6% and 3.6%, respectively.[11] Observational studies have shown a U-shaped, L-shaped or J-shaped association between BMI and mortality in Japan and other Asian countries.[12–14] Nevertheless, there is little evidence regarding the influence of either high or low BMI and weight change.

To better understand weight change for Japanese individuals with low BMI and its association with specific-cause mortality, we conducted a large prospective study that included 88 419 men and women across Japan with a median 12.9 years of follow-up.

METHODS

Study population

Our subjects were 42 242 men and 46 177 women aged 40–69 years who had no history of ischaemic heart disease, stroke or cancer and who were available for reports on weight change in the Japan Public Health Center (JPHC)-based prospective study. The JPHC study consisted of cohorts I and II, which began in 1990 and in 1993, respectively, as described elsewhere.[12 15] In brief, the cohort I and II populations were residents aged 40–59 years in five public health centre (PHC) areas (Ninohe PHC of Iwate Prefecture, Yokote PHC of Akita Prefecture, Saku PHC of Nagano Prefecture, Chubu PHC of Okinawa Prefecture and Katsushika PHC of Tokyo) and residents aged 40–69 years in six PHC areas (Mito PHC of Ibaraki Prefecture, Nagaoka PHC of Niigata Prefecture, Suita PHC of Osaka Prefecture, Chuo-higashi PHC of Kochi Prefecture, Kamigoto PHC of Nagasaki Prefecture and Miyako PHC of Okinawa Prefecture), respectively. The entire population included 140 420 men and women. Of them, 113 461 individuals answered the self-report questionnaire. From that group, 88 419 were available for our analysis based on the inclusion criteria mentioned above (response rate 78%). The present study was approved by the Ethics Committee of the National Cancer Center.

Measurements

We assessed demographic characteristics, including height, weight, medical history, smoking habits and regular alcohol drinking, using a self-administered questionnaire at baseline. The amount of ethanol consumed per week was evaluated by measuring the weekly frequency and the type of alcoholic beverage (beer, sake, whiskey, shochu and wine). Histories of hypertension and diabetes were ascertained by the question, "Have the following conditions been diagnosed by physicians?", with a

list of hypertension, diabetes and other chronic diseases as potential responses.

Weight change in cohort I was determined by the question, "Any changes of your weight (more than 5 kg) since the age of 20?", with potential responses of loss, no changes or gain. In cohort II, participants were asked, "What was your weight when you were 20 years old?" We computed the weight change from the difference between the weight reported at age 20 and at baseline. A total of 47 856 individuals (22 520 men and 25 336 women) from cohort I and 40 563 individuals (19 722 men and 20 841 women) from cohort II who reported that their weight had changed since age 20 were included in the analysis of weight change.

The following variables were used as covariates with dummy variables: non-smoker, light smoker (<20 cigarettes/day) and heavy smoker (≥20 cigarettes/day); sports and physical exercise (≥1 day/week, other); those who took drugs (hypertension, hyperlipidaemia, diabetes, gout); and those who had been diagnosed by a doctor (hypertension, diabetes, gastroduodenal ulcer, liver disease and kidney disease). Alcohol intake per week was estimated from the frequency and amount of alcohol consumed as defined by the ethanol concentration of major alcoholic beverages. These values were classified into categorical variables using a traditional portion in Japan: non-drinker, 1–23 g/day, 23–46 g/day, 46–69 g/day and ≥69 g/day.[16] These groups correspond to the categories related to incident cardiovascular disease (CVD) among Japanese. All variables were assessed with a self-administered questionnaire.

The underlying cause of death was determined based on death certificates and coded by the International Classification of Diseases, ninth revision (ICD-9) until 1995, and translated into the corresponding ICD-10 codes or coded by the ICD-10 after that. Deaths from cancer were defined as C00–C97, and deaths from CVD were defined as I20–25 and I60–69 (ICD-10).

Statistical analysis

With a median 12.9 years of follow-up from 1990 (cohort I) and 1993 (cohort II) to the end of 2005, person-years were calculated as the period from the date of the baseline to that of the first endpoint (death, emigration or loss) or to 31 December 2005. Among the participants, 25 moved out of Japan, one withdrew participation and 248 (0.3%) were lost to follow-up.

Weight change was classified into three comparable categories between cohorts I and II: loss (≥5 kg), stable (change <5 kg) and gain (≥5 kg). Furthermore, in the cohort II subjects, we reclassified weight change into five categories to analyse a dose–response relationship between weight change and mortality risk: loss ≥10 kg, loss 5–9 kg, stable (change <5 kg), gain 5–9 kg and gain ≥10 kg.

Sex-specific hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated after adjusting for age (continuous); current BMI; smoking status (non-smoker, <20 cigarettes/day and ≥20 cigarettes/day); ethanol intake (non-drinker, 1–23 g/day, 23–46 g/day, 46–69 g/day and ≥69 g/day); sports and physical exercise; medications or past history of hypertension and diabetes; and past history of liver disease and kidney disease as dummy variables, stratified by the JPHC communities and age groups of 40–49 years, 50–59 years and 60–69 years to adjust for an exposure period of weight change since age 20, using Cox's proportional hazard models. A test for linear trends was also carried out using a weight change variable (continuous) adjusted for the same covariates. Statistical significance was assumed at $p<0.05$. SAS software, V.9.1 (SAS Institute, Inc., Cary, North Carolina, USA), was used for all analyses.

RESULTS

During a median 12.9 years of follow-up, we documented 6494 deaths among 42 242 men and 46 177 women from combined cohorts I and II, including 2888 deaths from cancer, 1011 from CVD and 2595 from other causes. Figure 1 shows sex-specific mortality rates from all causes, cancer, CVD and other causes among individuals according to the category since age 20 by age group. It clearly illustrates high mortality rates from any cause for subjects with weight loss in each age group.

Table 1 shows population characteristics by weight change category and p values for differences among them. Those who reported weight loss ≥5 kg since age 20 indicated lower BMIs at baseline and higher BMIs at age 20; these data were available only for cohort II subjects. The percentages of smokers or those who had a past history of and had taken medication for diabetes were higher in men and women with weight loss. Significant differences between groups were recorded for most of the variables investigated, except for alcohol intake and gout in women.

Table 2 shows sex-specific multivariable-adjusted HRs for the cause of death comparing respondents with those with stable weight as a reference group. In men, an inverse association between weight gain and mortality was found for all-cause mortality, cancer mortality and other causes of mortality. HRs for all-cause mortality in the multivariable model were 1.44 (95% CI 1.32 to 1.56) and 0.89 (95% CI 0.82 to 0.97) for men with weight loss and weight gain, respectively. Those for all-cause mortality and other causes of mortality were likely to be high in the younger age group, and those for cancer mortality increased in older men. There was no increased risk of death among men with weight gain. In women, the multivariable model indicated an L-shaped association and an elevated risk of death for those with weight loss (1.33; 95% CI 1.17 to 1.52); however, risks of cancer and CVD were not increased significantly. Similar to men, the HRs for other causes of death were increased in younger women with weight loss. The association of weight gain with mortality was not clear. We analysed results after deletion of the first 5 years of follow-up and computed similar HRs for weight loss and gain (data not shown). Although each risk was somewhat attenuated, the elevated mortality risks for men and women with weight loss were almost the same.

In the subgroup analyses (table 3), as for the relationship of illnesses and smoking status with mortality, men and women with weight loss who were not ill and men and women with weight loss who smoked were at risk of mortality from all causes, cancer (men only) and other causes. Men who smoked or had illnesses were also at increased mortality risk.

Table 4 shows multivariable-adjusted HRs of weight change categories for death from all causes, cancer, CVD and other causes, stratified by baseline BMI (<18.5 kg/m^2, 18.5–24.9 kg/m^2 and ≥25 kg/m^2). The reference group was the 18.5–24.9 kg/m^2 baseline BMI group and stable weight change. In any group, HRs seemed to be increased significantly among individuals with weight loss. The highest HRs for all causes were found in persons with both baseline BMI <18.5 kg/m^2 and weight loss (≥5 kg).

Since we obtained self-reported weights at study entry and at age 20 from individuals in cohort II, we calculated multivariable-adjusted HRs for all-cause mortality classified into five weight change categories by BMI at age 20 (fig 2). Regardless of whether an individual was overweight at age 20, weight loss ≥10 kg was a risk factor for mortality. Among non-overweight

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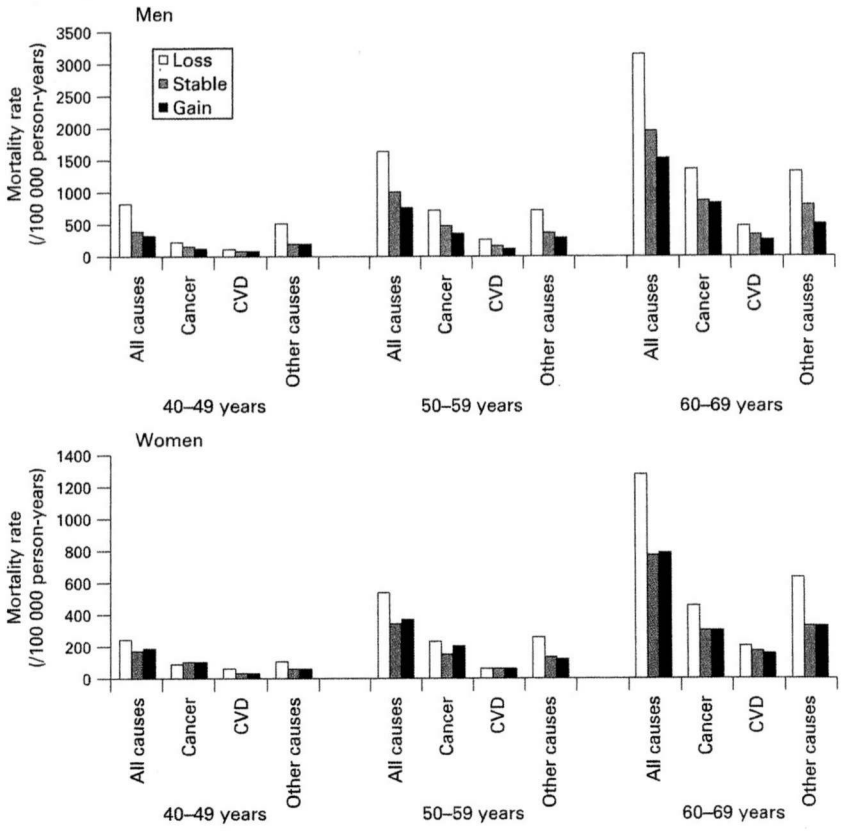

Figure 1 Sex-specific mortality rates from all causes, cancer, CVD and other causes among individuals with weight loss ⩾5 kg, stable weight (change, <5 kg) and weight gain ⩾5 kg since age 20 by age group.

Table 1 Population characteristics by sex and weight change categories since age 20

	Men				Women			
	Weight change since age 20				Weight change since age 20			
	Loss ⩾5 kg	Stable, change <5 kg	Gain ⩾5 kg	p Value	Loss ⩾5 kg	Stable, change <5 kg	Gain ⩾5 kg	p Value
Number	5159	14 338	22 745		5852	14 522	25 803	
Age, years	55.1	50.6	49.1	<0.001	52.1	49.4	49.9	<0.001
Baseline body mass index, kg/m²	21.5	22.0	25.0	<0.001	21.0	21.6	24.8	<0.001
Body mass index at 20,* kg/m²	24.4	21.8	21.0	<0.001	24.1	21.3	20.3	<0.001
Smoking status, %								
Non-smoker	35.5	41.0	52.4	<0.001	89.3	91.7	92.8	<0.001
<20 cigarettes/day	19.0	15.0	11.8		6.9	5.8	4.4	
⩾20 cigarettes/day	45.5	43.9	35.9		3.8	2.5	2.8	
Alcohol intake, g/week	212.0	209.3	202.5	<0.05	18.0	18.1	19.7	0.189
Sports and physical exercise, %								
⩾1 day/week	16.6	19.1	20.5	<0.001	15.7	19.7	18.8	<0.001
Persons who took drugs for, %								
Hypertension	13.8	8.8	12.3	<0.001	9.9	7.4	13.6	<0.001
Hyperlipidaemia	1.0	1.0	2.0	<0.001	1.7	1.5	2.4	<0.001
Diabetes	5.4	1.6	1.6	<0.001	2.1	0.8	1.2	<0.001
Gout	1.2	0.9	2.0	<0.001	0.4	0.2	0.3	0.054
Persons who had been diagnosed by a doctor with, %								
Hypertension	17.0	12.4	18.0	<0.001	10.6	9.2	16.5	<0.001
Diabetes	11.0	4.8	5.6	<0.001	3.6	1.7	2.8	<0.001
Liver disease	3.3	2.2	2.4	<0.001	1.1	0.8	0.9	<0.05
Kidney disease	2.8	2.1	1.9	<0.001	2.6	1.9	2.2	<0.001
Other illnesses†	23.8	18.6	17.3	<0.001	14.8	12.6	12.6	<0.001

*Data were available for 19 677 men and 20 786 women in cohort II.
†Includes any of asthma, allergy, stomach ulcer and gallstone.

Table 2 Sex- and age-specific number of deaths and multivariable-adjusted HRs of individuals with weight loss and weight gain since age 20 for death from all causes, cancer, CVD and other causes

		Men						Women					
		Loss ≥5 kg		Stable, change <5 kg		Gain ≥5 kg		Loss ≥5 kg		Stable, change <5 kg		Gain ≥5 kg	
Cause of death	Age group	Deaths	HR* (95% CI)	Deaths	HR	Deaths	HR* (95% CI)	Deaths	HR* (95% CI)	Deaths	HR	Deaths	HR* (95% CI)
All causes	All	1148	1.44 (1.32 to 1.56)	1530	1.0	1747	0.89 (0.82 to 0.97)	418	1.33 (1.17 to 1.52)	563	1.0	1088	0.98 (0.87 to 1.10)
	40–49	125	1.61 (1.31 to 1.98)	355	1.0	527	0.89 (0.76 to 1.05)	72	1.21 (0.91 to 1.61)	164	1.0	302	0.84 (0.68 to 1.05)
	50–59	573	1.41 (1.26 to 1.58)	788	1.0	941	0.88 (0.79 to 0.98)	209	1.33 (1.10 to 1.61)	265	1.0	599	1.01 (0.86 to 1.19)
	60–69	450	1.35 (1.16 to 1.58)	387	1.0	279	0.92 (0.77 to 1.11)	137	1.36 (1.04 to 1.74)	134	1.0	187	1.11 (0.86 to 1.44)
Cancer	All	471	1.27 (1.12 to 1.44)	678	1.0	769	0.90 (0.80 to 1.02)	162	1.17 (0.96 to 1.44)	262	1.00	546	1.04 (0.88 to 1.23)
	40–49	33	1.20 (0.82 to 1.77)	129	1.0	188	0.92 (0.70 to 1.20)	25	0.80 (0.50 to 1.26)	89	1.0	154	0.97 (0.71 to 1.31)
	50–59	244	1.27 (1.07 to 1.50)	383	1.0	434	0.84 (0.72 to 0.98)	89	1.26 (0.95 to 1.67)	123	1.0	320	1.11 (0.88 to 1.40)
	60–69	194	1.34 (1.06 to 1.68)	166	1.0	147	1.13 (0.87 to 1.46)	48	1.44 (0.95 to 2.18)	50	1.0	72	0.95 (0.62 to 1.44)
CVD	All	169	1.34 (1.09 to 1.66)	233	1.0	281	0.81 (0.66 to 0.99)	63	1.22 (0.87 to 1.71)	92	1.0	173	0.82 (0.62 to 1.10)
	40–49	16	1.19 (0.68 to 2.09)	59	1.0	89	0.82 (0.55 to 1.21)	18	1.74 (0.92 to 3.27)	25	1.0	46	0.56 (0.33 to 0.96)
	50–59	86	1.37 (1.03 to 1.84)	111	1.0	148	0.82 (0.62 to 1.10)	24	1.02 (0.60 to 1.72)	39	1.0	90	0.93 (0.61 to 1.42)
	60–69	67	1.30 (0.89 to 1.90)	63	1.0	44	0.72 (0.46 to 1.13)	21	1.12 (0.60 to 2.07)	28	1.0	37	1.18 (0.66 to 2.12)
Other causes	All	508	1.66 (1.47 to 1.89)	619	1.0	697	0.92 (0.81 to 1.05)	193	1.56 (1.27 to 1.91)	209	1.0	369	0.97 (0.80 to 1.18)
	40–49	76	2.06 (1.56 to 2.72)	167	1.0	250	0.90 (0.72 to 1.14)	29	1.60 (1.00 to 2.56)	50	1.0	102	0.91 (0.62 to 1.33)
	50–59	243	1.60 (1.34 to 1.91)	294	1.0	359	0.97 (0.81 to 1.16)	96	1.53 (1.14 to 2.04)	103	1.0	189	0.91 (0.69 to 1.20)
	60–69	189	1.39 (1.10 to 1.76)	158	1.0	88	0.78 (0.57 to 1.06)	68	1.43 (0.98 to 2.10)	56	1.0	78	1.23 (0.83 to 1.85)

*HR was adjusted for age; current body mass index; smoking status (non-smoker, <20 cigarettes/day and ≥20 cigarettes/day); alcohol intake (non-drinker, 1–23 g/day, 23–46 g/day, 46–69 g/day and ≥69 g/day); sports and physical exercise; medications or past history of hypertension and diabetes; and past history of liver disease and kidney disease stratified by JPHC communities and age groups of 40–49 years, 50–59 years and 60–69 years (only for all age groups).
CVD, cardiovascular disease.